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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,637	11/25/1997	ELAZAR RABBANI	ENZ-53(DIV5)	4643

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/978,637	RABBANI ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/18/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *318-323* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 November 1997* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/11/08, 1/14/08, 1/14/08, 1/14/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 245,248-251,253-255,260,264,265,268,270,272,284,288-290,296,299,303,304,308-313 and 318-325.

Continuation of Disposition of Claims: Claims rejected are 245,248-251,253-255,260,264,265,268,270,272,284,288-290,296,299,303,304,308-313,324 and 325.

DETAILED ACTION

Status of Application/Amendment/Claims

With regards to the supplemental election of species requirement mailed n 12/28/07, applicant's election with traverse of "snRNA promoter" in claim 325 in the reply filed on 1/18/08 is acknowledged. The traversal is on the ground(s) that it would not be undue burden to search the two species. This is not found persuasive because each of the types of promoters are structurally distinct, each requiring a separate and distinct search.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's response filed 10/9/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 4/4/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant has added claim 325. Therefore, claims 245,248-251,253-255,260,264,265,268,270,272,284,288-290,296,299,303,304,308-313 and 318-325 are pending in the instant application.

This application contains claims 318-323 drawn to an invention withdrawn by original presentation with traverse in the action mailed on 2/11/04. A complete reply to

the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's amendments to the claims filed on 10/9/07, with respect to the rejection(s) of claim(s) under 35 U.S.C. 112, 2nd paragraph, 35 U.S.C. 102(b) and (e), and 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, the rejections have been withdrawn.

However, upon consideration of the claim amendments filed on 10/9/07, new ground(s) of rejection are made as explained below.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 1/11/08 and 1/14/08 have been considered by the examiner.

Response to Claim rejections -- 35 USC § 112

Claims 265, 268, 270, 272, 284, 288-290, and 296, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, as explained in the office action mailed on 4/4/07. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION.**

Claim 265 recites, "said antisense nucleic acid sequence replacing sequences that participated in stem-loop formation in said snRNA". Although Figure 41 depicts a

U1 with antisense sequence inserted, there is not support for molecules having each of the characteristics of claim 265 and an antisense nucleic acid sequence that replaces sequences that participated in stem-loop formation in any snRNA, as instantly recited. Claims 268, 270, 272, 284, 288-290, and 296 are rejected because they depend from claim 265.

Applicant argues that Figure 41 displays an antisense sequence replacing sequences that participate in stem-loop formation. The example if Figure 41 does not offer support for the specific terminology or breadth that is recited in instant claim 265. Applicant also points to text in the specification for support for the claim language. Applicant points to Example 26 on page 182 for an example of Bcl I and Bsp E1 being used to remove a 49 base segment of the U1. This specific example pointed to by applicant does not offer support for the broad language of the instant claims, which is not directed to the specifics of the example. The specification does not disclose support commensurate in breadth with the instant claim language.

There is no support for this claim limitation in the claimed priority documents. Therefore, the effective filing date of claims 265, 268, 270, 272, 284, 288-290, and 296 is considered, for purposes of prior art, to be 11/25/97, which is the filing date of the instant application.

Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation added in the amended claims filed on 12/26/2006.

New Objections/Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 245-255, 260, 264, 299, 303, 304, 308-313, 324 and 325 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION.**

Claim 245 recites that the secondary nucleic acid or gene product "does not act as a template for the synthesis of said primary nucleic acid". However, the instant specification does not disclose this limitation.

Claim 299 recites that the isolated multi-cassette nucleic acid construct comprises “at least three promoters and/or at least three initiators”. However, the instant specification does not disclose this limitation.

Claims 246-255, 260, 264, 303, 304, 308-313 and 324 are rejected because they depend from claim 245 or claim 299.

Newly added claim 325 is not fully supported by the specification. The specification does not teach isolated multi-cassette nucleic acid constructs comprising either more than one promoter or more than one initiator or both, wherein said promoter

is a snRNA promoter or bacteriophage promoter which upon introduction into a eukaryotic cell produces more than one specific nucleic acid, each such specific nucleic acid being substantially nonhomologous to each other and being either complementary with a specific portion of one or more viral or cellular RNAs in a cell or binds to a specific viral or cellular protein, wherein each specific nucleic acid binds to different target nucleic acid sequences. The specification does not teach the combination of each of these specific elements.

There is no support for this claim limitation in the claimed priority documents. Therefore, the effective filing date of claims 245-255, 260, 264, 299, 303, 304, 308-313, 324 and 325 is considered, for purposes of prior art, to be 11/25/97, which is the filing date of the instant application.

A review of the specification does not reveal support for where the various claim amendments are found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation added in the amended claims filed on 10/9/07.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 299, 303, 304, 308-313, and 324 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calabretta et al. (US 5,734,039), in view of Binkley et al. (Nucleic Acids Research, 1995, Vol. 23, No. 16, pages 3198-3205), and Craig et al. (WO 95/08635) (these three references have been cited and are of record on the PTO-892 mailed 4/4/07).

The invention of the above claims is directed to an isolated multi-cassette nucleic acid construct comprising at least three promoters and/or initiators, which upon introduction into a eukaryotic cell produces at least one specific nucleic acid from each of said promoters or initiators, each such specific nucleic acid so produced being substantially nonhomologous with each other and being either complementary with a specific portion of one or more viral or cellular RNAs in a cell or binds to a specific viral or cellular protein, wherein each specific nucleic acid binds to different target nucleic acid sequences. The specific nucleic acid binds to a specific cellular protein comprising a localizing protein or a decoy protein. The specific nucleic acid binds to a specific cellular protein comprising a localizing protein or a decoy protein.

Calabretta et al. teach a composition for introducing two different antisense oligonucleotides specific for two different genes to a cell. Calabretta et al. teach a nucleic acid construct comprising a first promoter segment and a segment containing DNA of a cytoplasmic oncogene or proto-oncogene DNA, and a second promoter segment and a segment containing DNA of a nuclear oncogene or proto-oncogene. The DNA containing segments are in inverted orientation such that transcription of the DNA produces RNA complementary to the two mRNA transcripts of the two oncogene targets (see columns 8 and 9, for example). Calabretta et al. teach various modifications of the nucleic acids and teach means of delivery of the compositions.

Calabretta et al. do not teach introducing three or more sequences, do not tech nucleic acids that bind to cellular proteins and do not teach decoy proteins.

Binkley et al. teach high affinity RNA ligands to human nerve growth factor (NGF), which is a protein that is essential for growth, differentiation and maintenance of neurons and has the ability to localize or attract NGF-sensitive growing axons. Binkley et al. teach that the SELEX procedure is a widely used technique for isolating, identifying, and characterizing RNAs with high specificity and affinity to proteins. Binkley et al. teach that specific RNA ligands to proteins can be isolated using SELEX.

Craig et al. teach the expression of viral decoy proteins under the control of a locus control region and teach that decoy proteins act as antagonists to natural proteins involved in the replication of the HIV virus. Craig et al. teach that a decoy protein can be used as a mutant of a transactivator protein that is capable of binding to the

transactivator-responsive site on the host or viral genome, yet is incapable of activating transcription (see pages 2 and 3, for example).

It would have been obvious to incorporate sequences for the production of three or more different antisense sequences rather than the two different antisense sequences of Calabretta et al.

It would have been obvious to incorporate RNA oligonucleotides that bind to proteins, as taught by Binkley et al. in place of the antisense oligonucleotides taught in the system of Calabretta et al. It would have been obvious to use the SELEX method to assay for RNA molecules that bind to a protein, as taught by Binkley et al. and to specifically use a decoy protein as the protein, as taught by Craig et al.

One would have been motivated to incorporate at least three promoters to produce at least three antisense sequences instead of the two promoters to produce two different antisense sequences as taught by Calabretta et al. to optimize the activity of the multi-cassette nucleic acid construct of Calabretta et al. Since Calabretta et al. teaches utilizing a multi-cassette nucleic acid construct to deliver sequences that are transcribed into two different active antisense nucleic acid molecules that act synergistically in the cell, one would have certainly been motivated to incorporate three or more promoters for the production of three or more antisense sequences as well, for the same exact reasons as utilizing two.

It would have been prima facie obvious to perform routine optimization to incorporate three or more promoters, as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions

> of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular amount of promoters used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

One would have been motivated to incorporate RNA oligonucleotides that bind to proteins instead of the antisense oligonucleotides in the system of Calabretta et al. because Binkley et al. teach that high affinity RNA ligands to proteins, such as NGF that localizes NGF-sensitive growing axons, can be easily isolated using the SELEX procedure and teach that such RNAs may furnish useful diagnostic tools for the study of proteins. Since both types of nucleic acid oligonucleotides are used to determine binding interactions, as evidenced by the teachings of Calabretta et al. and Binkley et al., one would have been motivated to express the RNA ligands taught by Binkley et al. in the system of Calabretta et al.

One would have been motivated to screen for resultant RNA aptamers against a decoy protein because Binkley et al. teach that high affinity RNA ligands to proteins can be easily isolated using the SELEX procedure and teach that such RNAs may furnish useful diagnostic tools for the study of proteins. Since Craig et al. teach that decoy proteins are proteins that are useful to serve as a mutant that is capable of binding to a preferred site but yet is incapable of activating transcription, one would have been

motivated to use the SELEX method of Binkley et al. to identify RNA ligands to any known protein, such as the decoy proteins of Craig et al.

One would have a reasonable expectation of success given that each of the nucleic acid molecules were known to bind with target molecules in a sequence specific manner, as evidenced by Calabretta et al. and Binkley et al. One would have a reasonable expectation of success to express the protein binding RNA molecules of Binkley et al. in the dual system of Calabretta et al., with the advantage of producing two different binding molecules at once.

One would have a reasonable expectation of success given that Craig et al. teach the benefits of decoy proteins and Binkley et al. teach assaying for RNA aptamers to proteins and teach a method (SELEX) that is widely use to identify RNA molecules that bind to known proteins.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 299, 303, 304, 308-313, 324 and 325 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calabretta et al. (US 5,734,039), in view of Binkley et al. (Nucleic Acids Research, 1995, Vol. 23, No. 16, pages 3198-3205), and Craig et al. (WO 95/08635) (these three references have been cited and are of record on the PTO-892 mailed 4/4/07) as explained in the rejection under 35 U.S.C. 103(a) above, further in view of Dietz (US 5,814,500).

The invention of the above claims is directed to an isolated multi-cassette nucleic acid construct comprising at least three promoters and/or initiators, which upon introduction into a eukaryotic cell produces at least one specific nucleic acid from each of said promoters or initiators, each such specific nucleic acid so produced being substantially nonhomologous with each other and being either complementary with a specific portion of one or more viral or cellular RNAs in a cell or binds to a specific viral or cellular protein, wherein each specific nucleic acid binds to different target nucleic acid sequences. The specific nucleic acid binds to a specific cellular protein comprising a localizing protein or a decoy protein. The specific nucleic acid binds to a specific cellular protein comprising a localizing protein or a decoy protein. The multi-cassette nucleic acid comprises a snRNA promoter.

Calabretta et al. does not teach constructs having a snRNA promoter.

Dietz teaches nucleic acid constructs for the delivery of antisense targeting sequences and teaches that preferably a snRNA promoter is included in the construct. Dietz teaches that the construct comprises stem loop structures that flank the antisense nucleic acid so that the antisense oligonucleotide can readily interact with any target sequence. Dietz teaches that the stem loops are preferably U1 snRNA stem loops and there is a cloning site into which virtually any antisense oligonucleotide could be inserted. Dietz teaches that the construct may be used to introduce sequences to create transgenic animals. Dietz teaches delivery of the construct to a cell and teaches a cell comprising the construct, as well as a biological system comprising the cell. For example, Dietz teaches that the constructs may be introduced into mice, rodents (e.g.

rat, hamster), rabbits, chickens, sheep, goats, fish, pigs, cattle, and non-human primates. Administration of the construct of the invention can be *in vivo*, *in vitro* or *ex vivo*.

It would have been obvious to incorporate the snRNA promoter of Dietz into the constructs of Calabretta et al.

One would have been motivated to incorporate a snRNA promoter into the constructs of Calabretta et al. because Dietz teaches that this is a beneficial manner to achieve allele-specific targeting with antisense oligonucleotides. Both Calabretta et al. and Dietz et al. teach manners of delivering antisense oligonucleotide sequences to the cell with expression constructs and promoters. Therefore, it is considered design choice to utilize one known beneficial promoter rather than another known beneficial promoter. Calabretta et al. and Dietz both teach utilizing promoters to express antisense oligonucleotide sequences. Therefore, one would have been motivated to routinely optimize the construct by incorporating the U1 snRNA machinery as taught by Dietz.

It would have been prima facie obvious to perform routine optimization to incorporate elements of the snRNA machinery, as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular promoter used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. Each of the elements of Dietz was known in the art to benefit in the delivery of antisense nucleic acids to biological systems.

One would have a reasonable expectation of success given that each of the elements were known in the art to benefit the delivery of antisense nucleic acid sequences, as evidenced by the teachings of Calabretta et al. and Dietz. One would have a reasonable expectation of success that the promoter of Dietz would benefit the system of Calabretta as well.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755. The examiner can normally be reached on Monday-Thursday 6:30 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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